Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection and Chemotherapy 28 (2022) 1220–1224

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Note

Adverse events after BNT162b2 mRNA COVID-19 vaccination in health care workers and medical students in Japan

Takahiro Namiki [a,1,2], Shihoko Komine-Aizawa [b,*,1], Kazuhide Takada [b], Chika Takano [b], Quang Duy Trinh [b], Satoshi Hayakawa [b]

[a] Nihon University School of Medicine, Tokyo, Japan
[b] Division of Microbiology, Department of Pathology and Microbiology, Nihon University School of Medicine, Tokyo, Japan

ARTICLE INFO

Keywords:
COVID-19
Vaccination
mRNA vaccine
Adverse event

ABSTRACT

To control the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the promotion of vaccination is important. However, adverse reactions following vaccination remain a concern. To investigate adverse events in the vaccinated Japanese population, we conducted a survey-based study among health care workers, including medical doctors and nurses; other medical staff; and medical university faculty, staff, and students in a single medical school and affiliated hospital in Japan. In addition, we analyzed the association of different adverse events with individual factors (e.g., age, sex) by performing network analysis. While young age and female sex are often considered risk factors for more severe adverse events, the regression models showed neither age nor sex was associated with local injection-site reactions after the second dose in this study. In contrast to local reactions, systemic adverse events were associated with young age and female sex. However, myalgia was unique in that it was not associated with younger age even though the network analysis showed that myalgia was consistently related to arthralgia and belonged to the group of systemic events after both the first and second vaccine doses. Further study is needed to ensure safe and effective vaccination to aid in controlling the COVID-19 pandemic.

1. Note

Vaccination is one of the most critical methods to control outbreaks of infectious diseases. Several effective vaccines for COVID-19 have been developed, some of which have an efficacy of as much as 95%, and many countries have implemented vaccination programs [1]. However, various adverse reactions might occur following vaccination [2–4], and these vaccine-associated adverse reactions can cause vaccine hesitancy [5,6]. Therefore, to investigate adverse events in the vaccinated Japanese population, we conducted a survey-based study in a single medical school and affiliated hospital in Japan.

We conducted a cross-sectional survey using Google Forms from June 9 to June 21, 2021. The survey subjects were medical students, faculty members, and staff at Nihon University School of Medicine; nursing students and teachers at Nihon University Nursing School; pharmacy students and faculty members at Nihon University School of Pharmacy; and hospital staff of Nihon University Itabashi hospital and Nihon University Hospital. This study was approved by the Ethics Committee of Nihon University School of Medicine (Approval number: P21-06-0). All procedures were performed in accordance with the guidelines of our institutional ethics committee and adhered to the tenets of the Declaration of Helsinki. To examine which individual characteristics were associated with a specific adverse event, generalized linear models with logistic regression were constructed using R version 4.1.0 [7]. Age was analyzed as a continuous numerical variable, and the odds ratio (OR) of age represented a positive correlation if the OR>1, no correlation if the OR = 1, and a negative correlation if the OR<1. The OR for sex was obtained by comparison of females to males. All regression models were evaluated by the Hosmer–Lemeshow test. A p value < 0.05 was considered statistically significant for all analyses. We performed a network analysis to analyze in detail the relationship between each individual adverse event. For building networks, generalization of the Ising model presented with the IsingFit package of R [8] was used. This model is a binary equivalent of Gaussian approximation methods that

* Corresponding author. 30-1 Oyaguchikamicho Itabashi-ku, Tokyo, Japan.
E-mail address: aizawa.shihoko@nihon-u.ac.jp (S. Komine-Aizawa).
[1] Takahiro Namiki and Shihoko Komine-Aizawa contributed equally to this study.
[2] Current affiliation: Junior resident, Nihon University Itabashi Hospital.

https://doi.org/10.1016/j.jiac.2022.05.002
Received 20 January 2022; Received in revised form 20 April 2022; Accepted 6 May 2022
Available online 11 May 2022

applies to only two-state data; interactions are considered pairwise, and the data need to be cross-sectional [8–10].

Overall, we obtained 1756 responses, after the exclusion of people who did not consent and inconsistent vaccination status reports; 1711 of these responses were deemed appropriate for the analysis. Eighteen (1.1%) responders had never been vaccinated with BNT162b2, 1687 (98.5%) were vaccinated at least once and 1656 (96.8%) were vaccinated twice. The basic characteristics of the responders is given in Table 1.

The basic data are shown in Fig. 1. A total of 90.8% (n = 1531) and 86.7% (n = 1436) of participants experienced local and/or systemic adverse events after the first and second doses, respectively. The regression models showed that the total adverse events after the first dose were associated with female sex (OR = 1.93, p = 1.37 × 10^{-6}) (Table 2). The total adverse events after the second dose of BNT162b2 were associated positively with female sex (OR = 2.19; p = 6.05 × 10^{-6}) and negatively with age (OR = 0.98, p = 3.25 × 10^{-3}) (Table 2). The most common local reaction was pain at the site of vaccine administration (post-first dose, 82.5%; post-second dose, 77.5%) (Fig. 1). Female sex was associated with local adverse events, such as pain, redness, itching, and swelling after the first dose of the vaccine (Table 2). However, the associations disappeared after the second dose (Table 2). Local adverse events were most frequent between 12 and 24 h after vaccination (data not shown).

Similar to the results of previous reports, BNT162b2 vaccination was associated with various systemic events in our study (Fig. 1). Although local adverse events slightly decreased from 83.9% to 79.3% after the second dose, the incidence of systemic adverse events increased from 30.0% to 72.2% (Fig. 1). The most frequent systemic events were fatigue, fever, and headache. The frequency of these events increased after the second dose of the vaccine, from 19.6% to 53.6%, 8.6% to 48.8%, and 9.2% to 33.6%, respectively. The average self-reported maximum fever temperature was 37.7 °C (SD = 0.6) after the first dose and 38.2 °C (SD = 0.7) after the second dose. Regression analysis revealed that younger age was associated with fatigue, headache, fever, chills, arthralgia, nausea/vomiting, and abdominal pain after the second dose

Table 1
Characteristics of BNT162b2-vaccinated responders (n = 1687).

Characteristics	
Age in year	
1 Mean	33.1
2 Range	18–74
3 SE	13.7
Sex (%)	
Male	825 (48.9)
Female	856 (50.7)
Other	3 (0.2)
Occupation (%)	
1 Doctor	325 (19.3)
2 Nurse	73 (4.3)
3 Student	823 (48.8)
4 Other	454 (26.9)
Use of regular medication	382 (22.6)
Underlining/past medical disorders (%)	
Any kind of allergy	341(20.2)
Allergic reaction to previous vaccine(s)	34 (2.0)
Diabetes mellitus	9 (0.5)
Hypertension	10 (0.6)
Cardiovascular disorder	17 (1.0)
Cerebrovascular accident	2 (0.1)
Immune-mediated inflammatory disease	23 (1.4)
Malignancy	22 (1.3)
Asthma	39 (2.3)
Atopic dermatitis	7 (0.4)
Nonmalignant obstetrical and/or gynecological disorder	23 (1.4)
Nonasthmatic respiratory disorder	23 (1.4)
Gastrointestinal disorder	28 (1.7)
Hepatobiliary and/or pancreatic disorder	13 (0.8)
Urological disorder	2 (0.1)

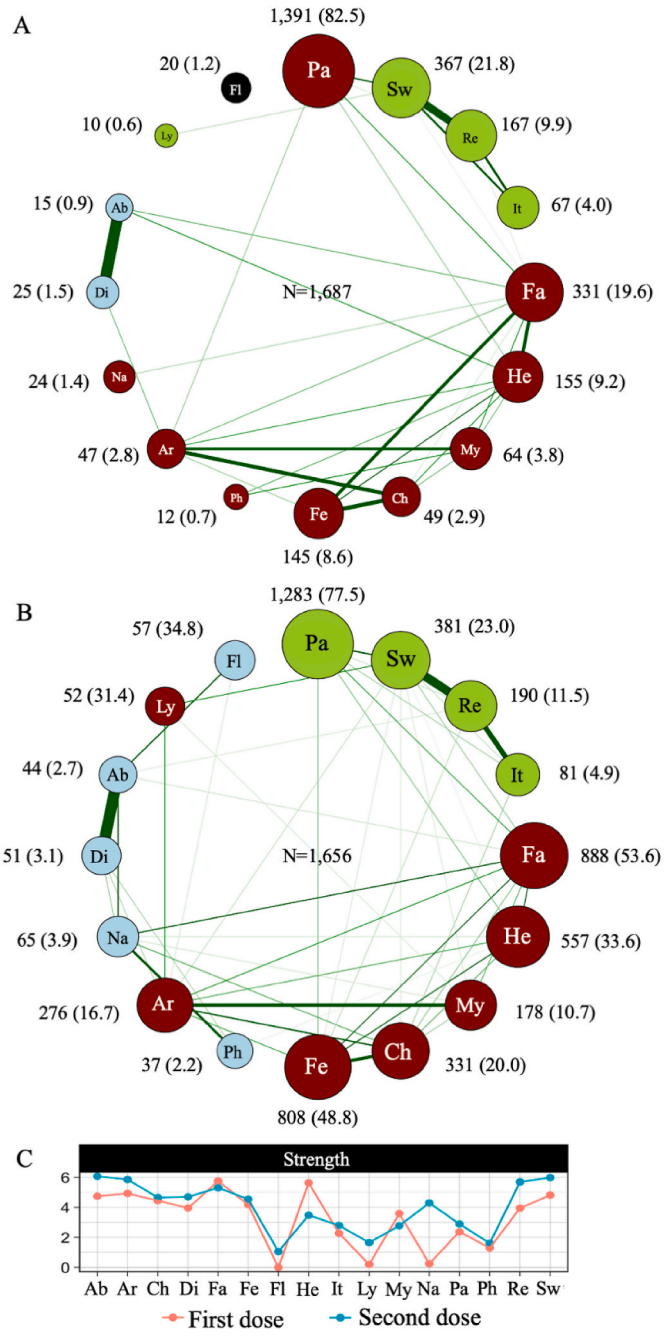

Fig. 1. The networks after the first and second doses of BNT162b2. Each circle (node) represents an adverse event. The number given near a circle represents the count of observed events, and within the parenthesis is its fraction in the total count of vaccinated persons for each dose. In networks of events after the first dose (A) and after the second dose (B), there were 3 common clusters of adverse events: (1) fatigue, headache, fever, myalgia, chills and arthralgia; (2) local swelling, local redness and local itching; and (3) abdominal pain and diarrhea. For the other events, there were inconsistencies among community distributions between the two networks, possibly due to the lack of observations, and there was also low strength of the nodes in the two networks (C). Ab; abdominal pain, Ar; arthralgia, Ch; chills, Di; diarrhea, Fa; fatigue, Fe; fever, Fl; facial flushing, He; headache, It; local itching, Ly; lymphadenopathy, My; myalgia, Na; nausea/vomiting, Pa; local pain, Ph; pharyngeal pain/irritation, Re; local redness, Sw; local swelling.

Table 2
The association age and sex and to adverse events after the first and the second dose of BNT162b2.

Variables			OR	95%CI	VIF	Z-value	P-value
Total events	First	Age	0.99	0.98–1.00	1.02	−1.35	0.177
		Sex (female) §	1.93	1.48–2.52	1.02	4.83	1.37×10^{-6} *
	Second	Age	0.98	0.97–0.99	1.05	−2.943	3.25×10^{-3} *
		Sex (female) §	2.19	1.57–3.09	1.02	4.53	6.05×10^{-6} *
Local pain	First	Age	1.00	0.99–1.01	1.02	−0.64	0.52
		Sex (female) §	1.59	1.22–2.07	1.01	3.4	6.50×10^{-4} *
	Second	Age	0.98	0.97–1.00	1.17	−2.76	5.85×10^{-3} *
		Sex (female) §	1.19	0.88–1.60	1.07	1.12	0.26
Local redness	First	Age	0.99	0.08–0.21	1.05	−1.91	5.64×10^{-2}
		Sex (female) §	1.47	0.97–1.00	1.01	2.25	2.46×10^{-2} *
	Second	Age	0.99	0.97–1.01	1.03	−1.15	0.25
		Sex (female) §	1.27	0.77–2.05	1.06	0.97	0.33
Itch	First	Age	0.98	0.96–1.00	1.01	−1.55	0.12
		Sex (female) §	2.68	1.55–4.84	1.01	3.41	6.44×10^{-4} *
	Second	age	0.99	0.95–1.03	2.79	−0.56	0.57
		Sex (female) §	0.97	0.49–1.91	1.19	-8.30×10^{-2}	0.903
Local swelling	First	Age	0.98	0.96–1.00	2.73	−2.56	1.04×10^{-2} *
		Sex (female) §	1.79	1.39–2.31	1.11	4.46	8.04×10^{-6} *
	Second	Age	0.98	0.96–1.01	2.66	−1.40	0.16
		Sex (female) §	1.02	0.70–1.50	1.15	0.12	0.90
Fatigue	First	Age	0.97	0.96–0.99	2.85	−3.23	1.25×10^{-3} *
		Sex (female) §	1.82	1.39–2.40	1.15	4.30	1.71×10^{-5} *
	Second	Age	0.97	0.96–0.98	2.93	−4.37	1.25×10^{-5} *
		Sex (female) §	1.52	1.20–1.91	1.16	3.52	4.35×10^{-4} *
Headache	First	Age	0.95	0.93–0.98	2.69	−3.78	1.54×10^{-4} *
		Sex (female) §	1.84	1.26–2.70	1.13	3.13	1.77×10^{-3} *
	Second	Age	0.96	0.95–0.98	2.79	−4.88	1.09×10^{-6} *
		Sex (female) §	2.05	1.60–2.63	1.17	5.63	1.76×10^{-8} *
Myalgia	First	Age	1.04	1.00–1.08	4.55	2.11	3.50×10^{-2} *
		Sex (female) §	2.26	1.28–4.14	1.12	2.75	6.05×10^{-3} *
	Second	Age	1.00	0.98–1.02	2.92	−0.19	0.85
		Sex (female) §	1.75	0.02–0.17	1.19	2.77	5.67×10^{-3}*
Chill	First	Age	0.92	0.88–0.960	2.30	−3.78	1.55×10^{-4} *
		Sex (female) §	1.61	0.85–3.15	1.13	1.45	0.15
	Second	Age	0.98	0.98–1.82	1.07	−3.68	2.37×10^{-4} *
		Sex (female) §	1.43	1.10–1.87	1.05	2.62	8.85×10^{-3} *
Fever	First	Age	0.95	0.92–0.96	2.78	−3.68	2.32×10^{-4} *
		Sex (female) §	1.38	0.94–2.03	1.11	1.645	9.95×10^{-2}
	Second	Age	0.98	0.97–0.99	2.71	−2.94	3.26×10^{-3} *
		Sex (female) §	1.72	1.37–2.16	1.16	4.65	3.34×10^{-6} *
Arthralgia	First	Age	0.99	0.96–1.01	1.01	−1.23	0.22
		Sex (female) §	1.71	0.94–3.22	1.01	1.73	8.33×10^{-2}
	Second	Age	0.97	0.96–0.99	2.82	−2.64	8.24×10^{-3} *
		Sex (female) §	2.15	1.57–2.97	1.18	4.71	2.48×10^{-6} *
Nausea/vomit	First	Age	0.99	0.94–1.04	2.36	−0.54	0.59
		Sex (female) §	4.23	1.50–13.83	1.28	2.59	9.62×10^{-3} *
	Second	Age	0.95	0.92–0.97	1.28	−3.67	2.46×10^{-4} *
		Sex (female) §	1.90	1.03–3.63	1.10	2.00	4.53×10^{-2} *
Diarrhea	First	Age	0.99	0.96–1.02	1.08	−0.70	0.49
		Sex (female) §	3.49	1.37–10.74	1.04	2.43	1.51×10^{-2} *
	Second	Age	0.95	0.90–1.00	3.01	−1.90	5.79×10^{-2}
		Sex (female) §	1.67	0.82–3.48	1.19	1.40	0.16
Abdominal pain	First	Age	0.93	0.83–1.03	2.38	−1.24	0.22
		Sex (female) §	3.10	0.90–14.41	1.09	1.65	9.85×10^{-2}
	Second	Age	0.91	0.85–0.96	3.10	−2.91	3.57×10^{-3} *
		Sex (female) §	3.30	1.43–8.61	1.19	2.64	8.33×10^{-3} *
Lymphadenopathy	First	Age	0.97	0.91–1.02	1.10	−1.10	2.716E-01
		Sex (female) §	2.49	0.64–13.22	1.13	1.222	0.22
	Second	Age	0.99	0.96–1.01	1.10	−0.95	0.34
		Sex (female) §	2.25	1.15–4.64	1.05	2.30	2.15×10^{-2} *
Facial flush	First	Age	1.02	0.96–1.08	3.81	0.63	0.53
		Sex (female) §	2.28	0.85–6.85	1.12	1.58	0.11
	Second	Age	0.98	0.93–1.02	3.01	−1.06	0.29
		Sex (female) §	1.59	0.77–3.39	1.17	1.23	0.22

CI; confidence interval, OR; odds ratio, VIF; variance inflation factor. § sex was comparison of female to male, * statistical significance.

(Table 2). Female sex increased the odds for several events, such as fatigue, headache, fever, chills, arthralgia, nausea/vomiting, abdominal pain, myalgia, and lymphadenopathy. Extra-injection site adverse events appeared as early as an hour after vaccination and were the most frequent 12–24 h after vaccination (data not shown). Interestingly, myalgia was unique in that it was not associated with younger age even though the network analysis showed that myalgia was consistently related to arthralgia and belonged to the group of systemic events after both the first and second vaccine doses.

One of the most serious adverse events was an anaphylactic reaction. In the present study, 5 (0.3%) and 1 (0.0%) participants reportedly had anaphylactic reactions after the first and second doses of the vaccine, respectively.

There were 3 common groups of adverse events: (1) fatigue,

headache, fever, myalgia, chills and arthralgia (systemic event group); (2) local swelling, local redness and local itching (local event group); and (3) abdominal pain and diarrhea (gastrointestinal event group) (Fig. 1). Other adverse events changed groups between the first and the second networks. The strongest connection was seen between abdominal pain and diarrhea in both networks, and the connections between fatigue and headache, between arthralgia and myalgia, and between chills and fever were consistently strong in both networks. There was no significant difference in the overall strengths and structures of the two networks ($p = 0.075$ and 0.86 respectively).

In this study, we investigated adverse events associated with the BNT162b2 mRNA COVID-19 vaccine among staff and students affiliated with a single medical institute in Japan. We also investigated the relationship between the adverse events after the first and second vaccinations.

Previous reports showed that adverse events after vaccination were stronger in females than in males and in younger persons than in older persons [2,4]. Our results were generally consistent with these reports; however, local events after the second dose were mostly unrelated to age and sex. This was also shown clearly in the post-second dose network analysis, in which these local events formed a distinct community. Interestingly, although the network analysis revealed that myalgia belonged to the systemic event community and had a strong correlation with arthralgia after both the first and the second doses, it was not associated with younger age. In fact, myalgia after the first dose was positively correlated with age. This could be related to the fact that the vaccine was delivered directly into the muscle tissue. Direct exposure to mRNA and tissue damage caused by needle insertion might have contributed to a different reaction pattern that was not influenced by age. In addition, vaccination via intramuscular injection has not been popular in Japan. Furthermore, local reactions might be affected by anatomical sites or procedures [11]; thus, the frequency and strength of local reactions could be investigated in multicenter studies.

The network analysis revealed that the symptoms of each adverse reaction were divided into three major groups, such as local, systemic and gastrointestinal event groups. In particular, abdominal pain and diarrhea formed a separate group after both the first and second doses. After the second dose, facial flushing, pharyngeal pain/irritation and nausea/vomiting were included in this group. The change in groups between the first and second doses could be attributable to the lack of observation, as shown by the low strength value for these events after the first dose.

In this study, the frequency of fever increased after the second dose of the vaccine, from 8.6% to 48.8%. The frequency of fever in Japan seems higher than in overseas reports [4,12]. While most overseas surveys define fever as 38 °C or higher, we based our data on participants' self-reports. In Japan, some people consider a body temperature of 37 °C or higher or an increase in body temperature above one's normal temperature to be a fever. Therefore, the rate of fever in Japan may have been higher than in overseas data. Since normal body temperature differs from person to person, we considered that surveying subjective symptoms rather than body temperature would better reflect the severity of adverse reactions. Moreover, fever is also an early symptom of COVID-19, thus the participants might be nervous about their fever.

Although the mRNA vaccine is a novel vaccine platform [13], we have already used a variety of vaccines for the control of various infectious diseases, and the adverse reactions are different for each vaccine. Therefore, we should carefully observe the inoculants or patients after vaccination.

There are some limitations to our research. This study was conducted in a limited number of people in a single institution. Importantly, those who did not experience any events or who experienced mild events after vaccination(s) may have been less likely to answer the questionnaire; therefore, the frequency and severity of events could have been overestimated. However, the frequency of major events observed in our study was not significantly divergent from those in previous reports, and these forms of biases were unlikely to be significant enough to invalidate our results.

In conclusion, vaccination with the BNT162b2 vaccine was associated with various adverse events, as reported previously [2,3]. Reporting and analysis of COVID-19 vaccine data by sex or gender are still lacking [14]. Further study is needed to delineate the causative relationship between observed events and vaccination to improve the management of adverse events and the social acceptance of the COVID-19 vaccine during the current pandemic.

Author contribution statement

Conceptualization, Takahiro Namiki, Shihoko Komine-Aizawa, Kazuhide Takada, Chika Takano, Quang Duy Trinh, and Satoshi Hayakawa; Data curation, Takahiro Namiki, Shihoko Komine-Aizawa, and Kazuhide Takada; Formal analysis, Takahiro Namiki; Investigation, Takahiro Namiki, Shihoko Komine-Aizawa, and Kazuhide Takada; Methodology, Takahiro Namiki, Shihoko Komine-Aizawa; Project administration, Shihoko Komine-Aizawa; Supervision, Satoshi Hayakawa; Visualization, Takahiro Namiki, Shihoko Komine-Aizawa, and Kazuhide Takada, Writing—original draft, Takahiro Namiki, Shihoko Komine-Aizawa; Writing—review & editing, Kazuhide Takada, Chika Takano, Quang Duy Trinh, and Satoshi Hayakawa.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

We thank Prof. Gotoda T. (Dean of Nihon University School of Medicine), Prof. Ishihara H. (School Principal of Nihon University Nursing School), Prof. Kaneita Y., Prof. Gon Y., Prof. Kawana K., Prof. Nakayama T., Prof. Hao H., Prof. Takayama T., Prof. Takahashi S. (Nihon University School of Medicine), Prof. Toriyama M. (Dean of School of Pharmacy, Nihon University) and Prof. Hayashi H. (School of Pharmacy, Nihon University) for their support during this study. We thank American Journal Experts for editing the English language in this manuscript.

References

[1] Polack FP, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med Dec 31 2020;383(27):2603–15. https://doi.org/10.1056/NEJMoa2034577 (in eng).
[2] Menni C, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis Jul 2021;21(7):939–49. https://doi.org/10.1016/s1473-3099(21)00224-3 (in eng).
[3] Lee YW, et al. Adverse reactions of the second dose of the BNT162b2 mRNA COVID-19 vaccine in healthcare workers in Korea. J Kor Med Sci May 31 2021;36(21):e153. https://doi.org/10.3346/jkms.2021.36.e153. in eng).
[4] Urakawa R, et al. Impact of age, sex and medical history on adverse reactions to the first and second dose of BNT162b2 mRNA COVID-19 vaccine in Japan: a cross-sectional study. BMC Infect Dis 2022;22(1):179. https://doi.org/10.1186/s12879-022-07175-y.
[5] Roy B, Kumar V, Venkatesh A. Health care workers' reluctance to take the Covid-19 vaccine: a consumer-marketing approach to identifying and overcoming hesitancy. NEJM Catalyst Innovations in Care Delivery 2020;1(6).
[6] Nomura S, et al. Reasons for being unsure or unwilling regarding intention to take COVID-19 vaccine among Japanese people: a large cross-sectional national survey. Lancet Reg Health West Pac Sep 2021;14:100223. https://doi.org/10.1016/j.lanwpc.2021.100223 (in eng).
[7] Foundation TR. The R project for statistical computing. 2021. https://www.r-project.org/. [Accessed 18 May 2021].
[8] van Borkulo CD, et al. A new method for constructing networks from binary data. Sci Rep Aug 1 2014;4:5918. https://doi.org/10.1038/srep05918.
[9] Papachristou N, et al. Network analysis of the multidimensional symptom experience of oncology. Sci Rep Feb 19 2019;9(1):2258. https://doi.org/10.1038/s41598-018-36973-1.
[10] Dalege J, Borsboom D, van Harreveld F, van der Maas HLJ. Network analysis on attitudes: a brief tutorial. Soc Psychol Personal Sci Jul 2017;8(5):528–37. https://doi.org/10.1177/1948550617709827.

[11] Nakajima Y, et al. Establishing a new appropriate intramuscular injection site in the deltoid muscle. Hum Vaccines Immunother Sep 2 2017;13(9):2123–9. https://doi.org/10.1080/21645515.2017.1334747.
[12] Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. Eur Rev Med Pharmacol Sci Feb 2021;25 (3):1663–9. https://doi.org/10.26355/eurrev_202102_24877.
[13] Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov Apr 2018;17(4):261–79. https://doi.org/10.1038/nrd.2017.243.
[14] Vassallo A, et al. Sex and gender in COVID-19 vaccine research: substantial evidence gaps remain. Front Glob Womens Health 2021;2:761511. https://doi.org/10.3389/fgwh.2021.761511 (in eng).